

REMARKS

Reconsideration and withdrawal of the rejections of the claims, in view of the amendments and remarks herein, is respectfully requested. Claims 1-3, 12, 23, and 27 are amended, claim 35 is added, and claims 9-11 are canceled. The amendments are intended to advance the application and are not intended to concede to the correctness of the Examiner's position or to prejudice the prosecution of the claims prior to amendment, which claims are present in a continuation of the present application. Claims 1-7, 12-23, 27-32, and 34-35 are pending.

Claims 1-7, 9-20, 22-23, 27-32, and 34 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Monroe et al. (U.S. Patent No. 5,625,049) and Koci et al. (J. Virology, 74:6173 (2000)) and further in view of Mueller-Lantzsch et al. (U.S. Patent No. 5,858,723). Claim 21 was rejected under 35 U.S.C. § 103(a) as being unpatentable over Monroe et al., Koci et al. and Mueller-Lantzsch et al., and further in view of Kim et al. (WO 92/20803). These rejections are respectfully traversed.

The '049 patent relates to human astrovirus-2 nucleic acid (abstract). Uses for that nucleic acid are disclosed as providing purified antigenic polypeptide fragments, primers or probes, or in vectors (column 2, lines 45-62). It is disclosed that the antigenic fragments may be isolated from the whole antigen by chemical or mechanical description, or synthesized directly (column 5, line 57-62), e.g., in a recombinant system (column 5, line 66-column 6, line 3). Numerous expression systems are disclosed at column 6, line 45-column 7, line 65, i.e., microbial, yeast and mammalian based expression systems (not insect based expression systems). Methods of using antibodies reactive with human astrovirus-2 or human astrovirus-2 antigens are disclosed at column 8, line 42-column 10, line 14. The examples in the '049 patent describe the isolation and sequencing of human astrovirus sequences, and the comparison of those sequences with known sequences.

The '049 patent does not describe a viral protein-based assay that specifically detects animals exposed to turkey astrovirus-2.

Koci et al. disclose that detection of astrovirus in most species is limited to electron microscopy and fluorescent antibody detection in cultured cells but that those methods are time

intensive and vulnerable to differences in interpretation (page 79). The fluorescent antibody detection methods referred to by Koci et al. are those exemplified in Lee et al. (Lancet, 4:406 (1977) (of record), where human embryo kidney cells in culture were inoculated with fecal samples and 24 hours later, the cells were fixed, treated with human convalescent serum, and then with fluorescently labeled sheep anti-human antibodies. Fluorescence was detected using microscopy.

To address the deficiencies in EM and fluorescent antibody based methods to detect turkey astrovirus, Koci et al. describe a RT-PCR based method that detected turkey astrovirus sequences in enteric samples with primers from the viral capsid and polymerase genes (abstract and page 80).

The '723 patent discloses that polypeptides with sequences corresponding to a human endogenous retrovirus (HERV-K10) are useful for diagnosing seminoma (abstract). The polypeptides may be expressed recombinantly, e.g., in *E. coli* or insect cells (Figures 2 and 4), to yield HERV-K10 antigen (column 2, lines 41-46). Antigen, e.g., gag and/or env, is discussed as useful to detect HERV-K10 specific antibodies in patients (column 2, lines 12-35). It is also disclosed that insect cells expressing HERV-K10 gag or env were mixed with uninfected insect cells which were then fixed, and then mixed with sera from a variety of patients (Example 3a and Tables IIIA-B), and purified HERV-K10 gag or env was employed in an ELISA (Example 4). Note that the sera from healthy individuals, as well as individuals with a variety of disorders, reacted with insect cells expressing HERV-K10 gag or env.

The '723 patent does not teach or suggest assays to detect seroconversion due to virus infection (HERV-K10 is an endogenous virus like element).

WO 92/20803 discloses that five serotypes of human astrovirus have been identified (page 5, lines 33-34). The specification discloses methods for the isolation and expression of astrovirus genomic sequences. It is disclosed that astrovirus antigen can be used to identify anti-astrovirus antibodies in serum (pages 22-23), and anti-astrovirus antibodies can be used to detect astrovirus antigens (pages 24-25). It is disclosed that human astrovirus sequences were isolated from a lambda cDNA expression library using sera from astrovirus-immunized rabbits (Examples 3, 4 and 6). Example 7 discloses how to prepare anti-human astrovirus antibodies.

WO 92/20803 does not describe a viral protein-based assay that specifically detects animals exposed to turkey astrovirus-2.

The Examiner is reminded that:

[i]n order for the Examiner to establish a *prima facie* case of obviousness, three base criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on Applicant's disclosure. M.P.E.P. § 2142 (citing In re Vaeck, 947 F.2d 488, 20 U.S.P.Q.2d 1438 (Fed. Cir. 1991)).

The Examiner asserts that through a nucleotide and amino acid sequence comparison between turkey astrovirus-2 and human astrovirus-2, one of skill in the art would know how to use the methods in the '049 patent to test for turkey astrovirus-2 infection in animals. The Examiner continues asserting that the '723 patent teaches the efficacy of expressing large amounts of recombinant proteins with the baculovirus system in insect cells in addition to testing sera samples from subjects for antibody recognition of the recombinant protein. The Examiner concludes that the combination of the cited teachings would inspire one skilled in the art to screen subjects suspected of turkey astrovirus serotype-2 infection by testing sera with turkey astrovirus-2 antigen isolated from recombinant insect cells.

First, one of the cited documents is unrelated to astroviruses or their detection (the '723 patent).

Although the '049 patent (an effective filing date of 1993) and WO 92/20803 (an effective filing date of 1991) generally disclose methods of using human astrovirus-2 antigens, there is no data in either document showing that an assay which employs those antigens is useful to detect antibodies in a blood sample. That is particularly relevant because as late as 2000, Koci et al. report that detection of astrovirus in most species is limited to electron microscopy and fluorescent antibody detection in cultured (infected) cells but that those methods are time intensive and vulnerable to differences in interpretation (page 79). To address these problems,

Koci et al. developed a RT-PCR assay to detect turkey astrovirus-2 nucleic acid in enteric samples.

Further, there is no suggestion or motivation in the cited references to modify or combine the references. That is, a general teaching of human astrovirus sequences and their expression, and that astrovirus antigen might be used to detect anti-astrovirus antibodies (the '049 patent and WO 92/20803), in view of a disclosure of a successful RT-PCR assay to detect turkey astrovirus sequences in enteric samples (Koci et al.) and that the detection of astrovirus in most species is limited to electron microscopy and fluorescent antibody detection in cultured, infected cells (Koci et al.), provides no motivation, and arguably a teaching away, to prepare a viral protein-based assay that specifically detects animals exposed to turkey astrovirus-2, especially in view of the exquisite sensitivity of RT-PCR based assays. Moreover, the '723 patent does not supply what is missing in any of the '049 patent, Koci et al. or WO 92/20803, as it relates to an assay to detect an endogenous virus-like element, an antigen of which can be detected in the sera of controls and individuals with various disorders, i.e., it may lack specificity.

The Examiner appears to employ impermissible hindsight to arrive at Applicant's invention, picking detection of turkey astrovirus-2, rather than a human astrovirus or a human endogenous retrovirus, and choosing a recombinant viral protein-based assay rather than a nucleic acid-based assay, even though none of the '049 patent, Koci et al. or WO 92/20803 provide data showing that anti-astrovirus antibodies could be detected in blood using recombinant astrovirus protein. Moreover, none of the cited documents provides a viral protein and blood based assay that performs as well as a RT-PCR based assay (see Table 3 in the specification).

In this regard, the Examiner is requested to consider the Rule 132 Declaration enclosed herewith, executed by Dr. Stacey Schultz-Cherry, one of the co-inventors of the present application. In the Declaration, Dr. Stacey Schultz-Cherry states that there are a number of obstacles to overcome when designing a serological assay, including identifying the viral protein recognized by the immune response, expressing the recombinant protein of interest in the proper conformation for identification by antibodies, and determining the conditions to express the protein for identification by antibodies in a physiological sample, so as to result in an assay with sufficient specific binding and low non-specific binding. Notably, none of the '049 patent, Koci

et al., the '723 patent, or WO 92/20803 provide data evidencing a successful assay to detect seroconversion associated with viral infection, e.g., astrovirus infection.

Moreover, Dr. Stacey Schultz-Cherry states that avian serum is loaded with cholesterol which can make it tricky to design an assay that detects a molecule in avian serum.

Also, Dr. Stacey Schultz-Cherry notes that assays reported to detect human or turkey astroviruses detect virus infection by employing fecal or intestinal content samples (see paragraph 6 of the Declaration); not seroconversion. Thus, the reported assays are useful only during an infection while Applicant's assay detects exposure to virus even after the infection is over.

Accordingly, withdrawal of the § 103 rejections is respectfully requested.

CONCLUSION

Applicant respectfully submits that the claims are in condition for allowance and notification to that effect is earnestly requested. The Examiner is invited to telephone Applicant's attorney (612) 373-6959 to facilitate prosecution of this application.

If necessary, please charge any additional fees or credit overpayment to Deposit Account No. 19-0743.

Respectfully submitted,

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Date

November 30, 2006

By

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Name

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